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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/716,054 | 11/17/2000 | Gerald R. Crabtree | STAN-166 | 7611 |

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| EXAMINER | |
|---|---|
| COOK, LISA V | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1641 | |

DATE MAILED: 07/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/716,054 | CRABTREE ET AL. | |
| | Examiner | Art Unit | |
| | Lisa V. Cook | 1641 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *18 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *16-24 and 49-82* is/are pending in the application.

4a) Of the above claim(s) *56-64 and 77-82* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-24,49-55 and 65-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/18/06 has been entered.

### *Amendment Entry*

2. In the amendment filed 18 April 2006, claims 16, 49, and 56 were modified. New claims 65-82 were added. Currently claims 16-82 are pending.

### *Claim Status*

3. Applicant's previous response to the Final Office Action mailed April 19, 2005 and the telephonic interview, both dated 18 November 2005 are again acknowledged. Claims 56-64 were withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. Newly submitted claims 77-82 are dependent on the non-elected invention of claims 56-64. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 56-64 and 77-82 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

4. Currently claims 16-24, 49-55, and 65-76 are under consideration.

5. Rejections and/or objections of record not reiterated herein have been withdrawn.

*Please Note: The newly amended claims read on **in vitro** and **in vivo** methods. Accordingly, the claims were rejected under 112, 1st for reading on in vivo procedures and also rejected under 35 USC 102 and 103 for reading on in vitro procedures.*

## NEW GROUNDS OF REJECTIONS

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 16-24, 49-55, and 65-76 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Specifically claims 16-24, 49-55, and 65-76 are drawn to methods of inhibiting a binding event in a cell. The cell may exist in a host (*in vivo*) and a non-naturally occurring bifunctional inhibitor molecule is administered in an effective amount of to prevent access of a binding protein (P) to the target protein (T).

Although the specification is enabling for the production and *in vitro* utility of non-naturally occurring bifunctional inhibitor molecules (See assay design and results - pages 20-21), it does not reasonably provide enablement for inhibiting protein-protein interactions *in vivo* with said non-naturally occurring bifunctional molecule.

Firstly, the development of non-naturally occurring/synthetic bifunctional molecules with binding characteristics of interest necessitates several conditions, which have not been described in the instant specification.

In one instance, the prior art discloses that the development of inhibitors which can bind by both an active site specific interaction to a primary binding site and by a structure nonspecific hydrophobic interaction to a second site (bifunctional or bispecific molecules) requires several parameters to produce the intended binding specificity.

These parameters include; a crystal structure of the enzyme with the bound primary inhibitor, there must be a relatively "open" active site, to permit access to the active site, and the linker must not introduce few unfavorable enthalpic and entropic interactions into the bound state. See Jein et al., J Med Chem., 1994, 37, 2100-2105, especially scheme 1 and page 2103, 2nd column 2nd paragraph. These parameters have not been addressed by the instant disclosure. Therefore one of skill in the art would not be able to predict the inhibition by binding of the claimed bifunctional molecule *in vivo*.

Secondly, the specification fails to teach the use of the claimed bifunctional inhibitor molecules in a living organism or host, such that an effective inhibition response is generated. The art has established that the successful production of bifunctional molecules and their utility in assay protocols does not predict their behavior in living animals or a host.

In other words, the bifunctional molecule must be evaluated in a host in order to determine efficacy or inhibition effects. See Kuduk et al. Bio & Med Chemistry Letters, 10, 2000, 1303-1306, in particular page 1305, 2nd column Conclusion, 2nd paragraph.

Further, the art teaches that successful *in vitro* bifunctional construct binding is not always indicative of the *in vivo* results exhibited by that same bifunctional molecule.

For example, see Peipp and Valerius page 510 – Conclusion, wherein "Results from clinical trials (in vivo effective dosage) with bispecific antibodies are less encouraging". Peipp and Valerius, Biochemistry Society Transactions, 2002, Volume 30, part 4, pages 507-511.

Accordingly, the specification does not provide substantive evidence that the claimed bifunctional molecules are capable of inhibiting a protein-binding event *in vivo*. This demonstration is required for the skilled artisan to be able to use the claimed bifunctional molecules for their intended purpose of preventing protein binding.

Without this demonstration, the skilled artisan would not be able to predict the outcome of the administration of the claimed bifunctional or bispecific non naturally occurring compositions. The ability to reasonably predict the capacity of a single non -naturally occurring bifunctional molecule to prevent protein-protein interaction in vivo is problematic.

Unfortunately, the art is replete with instances where even well characterized compositions that induce an in vitro response fails to elicit *in vivo* utility. See Waldmann, Science, Vol.252, 21 June 1991, pages 1657-1662, in particular page 1657 – 2nd column, wherein antibodies binding therapy has proven elusive and only one monoclonal antibody has been licensed for clinical utility. Accordingly, the art indicates that it would require undue experimentation to formulate and use a successful binding composition with out prior demonstration of efficacy.

Thirdly, *in vivo* testing or administration to a host entails considerations for host/patient tolerance, differences, validation, and monitoring; which are not set forth in the disclosure.

The disclosure merely outlines that the non-naturally occurring bifunctional molecule may be used to treat a variety of diseases, including cellular proliferation, autoimmune disease, cardiovascular diseases, hormonal abnormality, infectious disease, and the like without any supporting data/experimentation. See page 19 lines 24-35.

However, Tockman et al. (Cancer Research 52:2711s-2718s, 1992) teach considerations necessary for a suspected cancer antibody biomarker (intermediate end point marker) to have efficacy and success in a clinical application. See page 2716s. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to other compositions being administered and tracked in a host/patient.

Tockman teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials, see abstract.

Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and **if validated** (emphasis added) can be used for population screening (p. 2713s, column 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease.

"This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point [marker]", see page 2714s, column 1, Biomarker Validation against Acknowledged Disease End Points section. Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials, see page 2716s, column 2, Summary section.

Tockman reiterates that the predictability of the art in regards to cancer prognosis and the estimation of life expectancies within a population with a disease or disorder are highly speculative and unpredictable. It has been set forth above that 1) the experimentation required to generate a non-naturally occurring bi-functional molecule which provides binding inhibition such that it would prevent target binding in a living host would be great as 2) there are no immunological experiments provided to demonstrate that the claimed bifunctional compositions are capable of mounting an efficient inhibition response and, more importantly, there are no challenge experiments to demonstrate that a person immunized with any one of the claimed compositions would be treated/protected from a disease.

There are no protocols provided which demonstrate which bifunctional molecules would be effective in immunization, nor are there any protocols detailing the amount of the bifunctional compositions needed to inhibit protein-protein interaction or mount a sufficient immune response in disease treatment, 3) there are no working examples provided in the instant specification, 4) the nature of the invention is a method for producing a non-naturally occurring bifunctional molecule which would provide binding inhibition and treatment in a host, 5) the relevant skill of those in the art is high yet 6) the state of the prior art has been shown to be highly unpredictable

as evidenced by prior art afore mentioned, and lastly 7) the claims broadly encompass the administration of compositions to a host (in vivo) to target protein prevent binding in the host, it is therefore set forth that one of skill in the art could not make and/or use the invention without undue experimentation.

Based on the analysis and the teachings presented above it would require undue experimentation for the skilled artisan to practice this invention because there is no support in the specification for the enablement of the broadly claimed invention.

Therefore, in view of the insufficient guidance in the specification, extensive experimentation would be required to enable the claims and to practice the invention as claimed.

7. Claims 16-24, 49-55, and 65-76 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the single bifunctional molecule complex FKBP-NFAT (see disclosure pages 20-22), it does not reasonably provide enablement for the use of any and all bifunctional molecules in the claimed methods. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The prior art discloses that the development of inhibitors which can bind by both an active site specific interaction to a primary binding site and by a structure nonspecific hydrophobic interaction to a second site (bifunctional or bispecific molecules) requires several parameters to produce the intended binding specificity.

These parameters include; a crystal structure of the enzyme with the bound primary inhibitor, there must be a relatively "open" active site, to permit access to the active site, and the linker must not introduce few unfavorable enthalpic and entropic interactions into the bound state. See Jein et al., J Med Chem., 1994, 37, 2100-2105, especially scheme 1 and page 2103, 2nd column 2nd paragraph. These parameters have not been addressed by the instant disclosure for all possible bifunctional molecules. Therefore, only FKBP-NFAT meets the claim limitation but not any and all bifunctional molecules.

***Claim Rejections - 35 USC § 102***

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

I. Claims 16-24, 49-55, and 65-76 are rejected under 35 U.S.C. 102(a) as being anticipated by Briesewitz et al. (Proc. Natl. Acad. Sci, USA, Vol.96, pages 1953-1958, March 1999) as evidenced by Briesewitz et al.(WO 99/61055).

Briesewitz et al. (Proc. Natl. Acad. Sci) disclose the bifunctional molecule SLFpYEEI and FKpYEEI. These bifunctional molecule is created by chemically linking a ligand of interest to another small molecule that binds tightly to a second protein. See abstract, page 1953 2nd column – Materials and Methods.

The peptides were synthesized, purified by HPLC, and stored in aqueous Tris/NaCl solution (pharmaceutical preparation). See page 1954 1st column. The bifunctional molecules were capable of binding to FKBP and the Fyn SH2 domain simultaneously to form a tetrapeptide complex. See page 1954, figure 1, and Table 1. The bifunctional molecules can be designed to increased binding affinity or to decrease binding or protein-protein interactions. See page 1956-figure 3 and page 1957-figure 4.

Briesewitz et al. (Proc. Natl. Acad. Sci) disclose that certain microorganisms use endogenous proteins to enhance their toxins. For example, cyclosporine and FK506 are bound by cyclophilin and FKBP respectively to inhibit the activity of calcineurin. The independent compounds of FK506 and cyclosporine have no measurable affinity for calcineurin alone. When they are complexed or apart of a bifunctional molecule they bind calcineurin with high affinity. See page 1953, 1st column 3rd paragraph.

Briesewitz et al. (Proc. Natl. Acad. Sci) are silent with respect to the size of the bifunctional molecule. In other words the reference does not specifically state that the bifunctional molecule is less than 5000 daltons. However, this limitation is deemed inherent to the SLFpYEEI and FKpYEEI structures as evidenced by Briesewitz et al. (WO 99/61055).

Both references to Briesewitz et al. disclose bifunctional molecules SLFpYEEI and FKpYEEI. While, Briesewitz et al. (WO 99/61055) teaches that these molecules are less than 5000 daltons. See Briesewitz et al. (WO 99/61055) page 6 lines 20-35, for example.

9. For reasons aforementioned, no claims are allowed.

10. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO fax center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 Fax number is (571) 273-8300, which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (571) 272-0816. The examiner can normally be reached on Monday - Friday from 7:00 AM - 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (571) 272-0823.

Any inquiry of a general nature or relating to the status of this application should be directed to Group TC 1600 whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see httpr//pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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